Soft Tissue Sarcomas

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One hundred fifty-five adult patients with "operable" soft part sarcomas including rhabdomyosarcoma, liposarcoma, leiomyosarcoma and fibrosarcoma of the trunk and extremities are reviewed. Local recurrences of 93% and 60% occurred after local and wide excisions of the primary tumor. In this series of patients, amputation was the most efficient procedure for controlling the primary site. The absolute 5 and 10-year survival rates for all four groups of tumors were 50% and 26%. Development of a second primary tumor of a different cell type occurred in 9% of the patients. Local recurrence, single distant metastasis, and/or second primary tumors should be considered potentially curable and appropriate surgical and/or radiation therapy carried out.

SOFT TISSUE SARCOMAS are infrequent neoplasms which often develop insidiously, and frequently present problems for both the pathologist in histologic classification and subsequently, the clinician in their management. Several factors are decisive in the initial selection of the most appropriate surgical procedure.

This report reviews our experience with 155 adult patients with operable soft tissue sarcomas treated at the Roswell Park Memorial Institute during the years 1950 through 1972.

Methods

The 155 patients included 40 with rhabdomyosarcoma, 40 with liposarcoma, 41 with fibrosarcoma and 34 with leiomyosarcoma of the soft somatic tissues of the trunk and extremities. Not included were tumors originating in the retroperitoneal tissues, genitourinary tract, and the head and neck areas, since the nature and surgical problems of sarcomas at these anatomical sites may be different.

Tumor recurrences confirmed by histological examination or by clinical studies were divided into the following categories: 1) *local*—referring to a recurrence within the previous surgical site or the immediate adjacent tissues; and 2) *distant*—defined as a recurrence in any site other than those tissues or muscle group of origin for the primary site, such as the lungs, central nervous system, viscera, and skeleton. A majority of the histological slides from all 155 patients were reviewed by Dr. John Pickren, Chief Pathologist at Roswell Park Memorial Institute, and co-author of this paper.

Five types of operations were used for treating the primary tumor depending on its size and anatomic site, namely: 1) radical amputation—defined as forequarter, hindquarter, or a disarticulation of the extremity at the hip or shoulder joint; 2) major amputation—removal of a major portion of an extremity such as above the knee or below the knee amputation; 3) wide excision—excision of the tumor with a three centimeter or more margin of normal tissue; 4) local excision—removal of the tumor with the "pseudocapsule" or less than one centimeter of normal tissue; and 5) local excision followed by a wide reexcision—excision of the previous surgical scar and a three centimeter area of normal tissue surrounding the area of the previous locally excised tumor, performed within 4 to 8 weeks of the local excision.

Clinical Manifestations

In this group of 89 males and 66 females, the age at the time of diagnosis ranged from 16 years to 80 years with a majority occurring between the ages of 40 and 70. These sarcomas presented as a painless enlarging mass in 120 of the 155 patients. In those patients presenting with pain, the pain was usually late in appearance and often mild in character.

The duration of the tumors before the patient sought medical attention varied from a maximum of 10 years to a minimum of 2 weeks, with an average period of 42 weeks. There was an average delay of 6 weeks before the defini-

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TABLE 1. *Anatomic Location of 155 Soft Tissue Tumors*

Histologic Type	Shoulder-Upper Arm	Lower Arm-Hand	Trunk	Hip-Upper Thigh	Above Knee-Foot	Total # Patients
Rhabdomyosarcoma	4	3	5	17	12	41
Liposarcoma	4	4	8	10	14	40
Fibrosarcoma	6	4	9	11	10	40
Leiomyosarcoma	6	4	8	6	10	34
Total # Patients	20	15	30	44	46	155

tive surgical procedure was performed. This delay is explained in part by the referral pattern of this Institute and multiple pathological consultations concerned with histological classification. Forty-five patients had two or more tissue diagnoses such as liposarcoma and fibrosarcoma, or rhabdomyosarcoma, leiomyosarcoma and undifferentiated sarcoma. In some instances the pathologist requested a second or third biopsy specimen.

The anatomic location of these 155 tumors is outlined in Table 1. The lower extremity was the prominent site in 90 patients for all 4 tumor groups.

Measurements of the primary tumor at the time of diagnosis were documented in 88 of the 155 patients; the smallest tumor was 1 x 1.5 cm and the largest was 12 x 28 cm. The average diameter of the tumors was 7 x 8 cm which illustrates dramatically the absence of pain which might prompt an earlier search for care. It is equally disturbing to find that the tumors in recent patients were as large, and the delay of treatment the same, as in those patients treated earlier in the study period.

Treatment and Results

For these 155 patients with soft tissue sarcomas, the 5 and 10-year absolute survival rates following all forms of therapy (which included surgery for the primary tumor and subsequent local and/or distant recurrences, and chemotherapy and/or radiation therapy for disseminated disease) are outlined in Figure 1. The 5 and 10-year average survival for all 4 tumor groups was 50% and 26%. For each individual group, the respective 5 and ten-year survival rates were: liposarcoma—65% and 28%; fibrosarcoma—55% and 38%; leiomyosarcoma—47% and 17%; and rhabdomyosarcoma—31% and 20%. Of interest are 27 patients (6 with fibrosarcoma, 9 with liposarcoma, 6 with rhabdomyosarcoma, and 6 with leiomyosarcoma) living with no evidence of tumor beyond 10 years and up to 20 years.

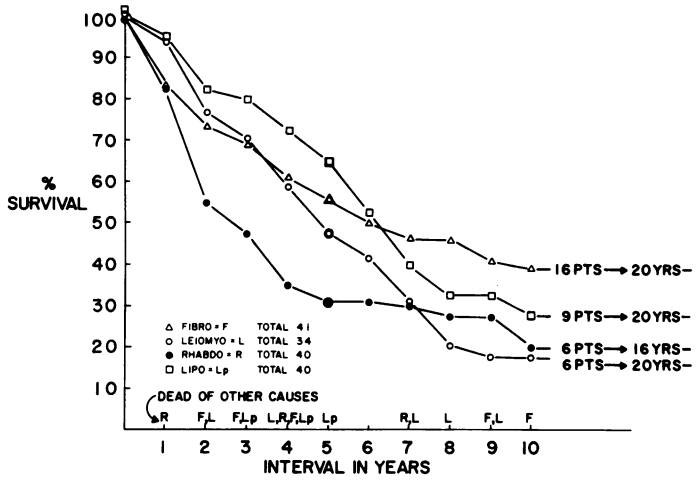

FIG. 1. This figure illustrates the absolute 5 and 10-year survival for each of the 4 types of soft tissue sarcomas following the initial treatment and all subsequent surgical procedures and other treatment, such as chemotherpay and radiation therapy.

The frequency of local and distant recurrences following the various surgical procedures for the primary lesion is summarized in Table 2. The pattern and recurrence rates, both local and distant, were similar for each of the 4 groups of tumors. Local recurrence occurred in 54 (93%) of 58 patients after *local* excision of the primary lesion and in 16 (73%) of 22 patients following wide re-excision of the primary area of a previously locally excised lesion. Local recurrence developed in 15 (60%) of 25 patients following *wide* excision of the primary lesion. Thirty-eight patients had major and/or radical amputations as the initial definitive surgical procedure for the primary tumor and failure to control the primary lesion occurred in 3 (8%) of these patients.

Nine patients received radiation therapy to the primary area following local excision of the primary tumor, and a local recurrence occurred in 4 (45%) of these patients. Two patients treated with radiation following wide excision of the primary lesion did not develop local recurrence.

Subsequent recurrences following surgical treatment of the first local recurrence are summarized in Table 2. A local recurrence occurred following local excision of the recurrent tumor in 29 of 33, or 88% of the patients; in 19 of 35, or 54% of the patients treated by wide excision; and in 2 of 11, or 18% of the patients treated by major and radical amputations.

Of the 155 patients, 121 had recurrent disease. The first recurrence was local only in 83 patients, distant in 29, both local and distant in 9. The fate of these patients is interesting. Of the 83 with local recurrences, several patients had two or more subsequent surgical procedures

TABLE 2. *First Recurrence Following Various Surgical Procedures for the Primary Tumor of Soft Tissue Sarcomas*

Surgical Procedure	*Fibrosarcoma* #Pts	LR	DR	Both*	*Leiomyosarcoma* #Pts	LR	DR	Both*	*Rhabdomyosarcoma* #Pts	LR	DR	Both*	*Liposarcoma* #Pts	LR	DR	Both*	Total LR	
LE	19	16(89%)**	2	1	15	12(93%)**	–	2	9	9(100%)	–	–	15	15(100%)	–	–	54/58	93%
LE → WE	4	3(75%)	–	–	8	4(50%)	1	–	7	6(100%)**	1	1	3	2(67%)	–	–	16/22	73%
WE	8	3(38%)	2	–	5	3(60%)	–	–	7	3(71%)**	1	2	5	2(60%)**	–	1	15/22	60%
Amp	5	–	3	–	3	1(67%)**	–	1	3	(33%)**	–	1	5	–	3	–	3/16	8%
Rad Amp	4	–	2	–	2	–	2	–	8	–	4	–	8	–	5	–	–	
LE → RT	–	–	–	–	–	–	–	–	6	3(50%)	2	–	3	1(33%)	–	–	4/9	45%
WE → RT	1	–	–	–	1	–	1	–	–	–	–	–	1	–	–	–	–	
Recurrences Following Surgical Treatment of the First Local Recurrence																		
LE	13	12(100%)**	–	1	6	4(83%)**	1	1	4	3(100%)**	–	1	10	6(70%)**	1	1	29/33	88%
WE	6	2(50%)**	1	1	11	2(45%)**	4	3	9	4(56%)**	3	1	9	4(67%)**	2	2	19/35	54%
Amp	1	–	1	–	–	–	–	–	1	–	–	–	1	–	–	–	–	
Rad Amp	–	–	–	–	3	–	–	–	4	1(50%)**	2	1	1	–	–	–	2/11	18%
LE → RT	1	–	–	–	–	–	–	–	3	–	3	–	–	–	–	–	–	

LR = local recurrence
DR = distant recurrence
LE = local excision
WE = wide excision
Amp = amputation
Rad Amp = radical amputation

LE → WE = local excision followed by wide excision
LE or WE → RT = local or wide excision followed by radiation

* *Both* = simultaneous local and distant recurrences
** % includes local recurrence of those patients with both local and distant recurrences

(local or wide excisions, or amputations) in an attempt to control the tumor at the primary site. The 5-year survival rates following surgical treatment of the first and/or all subsequent local recurrences were as follows: liposarcoma, 53%; fibrosarcoma, 43%; leiomyosarcoma, 53%; and 24% for rhabdomyosarcoma.

The first detectable recurrence was distant in 29 patients, the lung being the most common site of these metastases. Only two of these 29 patients survived more than 5 years; both patients are living free of disease for 15.9 and 17 years, respectively.

The first recurrence occurred simultaneously in local and distant sites in 9 patients. Of these 9, 4 died in less than 6 months and the other 4 died within 3.5 years from progression of disease.

A distant recurrence occurred in 38 or 24% (29 distant only, and 9 with both local and distant) of the 155 patients following the initial surgical treatment of the primary lesion. The incidence of distant recurrences following subsequent surgically treatable first, second, third and fourth recurrences were 30/83 (36%), 9/36 (25%), 4/15 (27%), and 3/8 (38%), respectively. In other words, persistence in providing adequate surgical excision of recurrent lesions is still successful in nearly two-thirds of the patients.

The time interval until the appearance of the first local recurrence following surgical therapy of the primary tumor is outlined in Fig. 2. Of the 155 patients, local recurrence occurred in 83 patients and of these, 71% were detected within one year and 82% within the first two years. However, prolonged followup is necessary, since the first local recurrence without evidence of distant disease occurred in one patient 10 years following the initial wide excision of a liposarcoma of the thigh. This patient has remained free of further recurrences for more than 3 years, following a wide excision of the local recurrence.

There are apparently various host factors which influence survival and Table 3 illustrates the variant biological interaction of rhabdomyosarcoma in two patients. The first patient, J.R., a 56-year-old Caucasian man, had 11 local recurrences, each treated by local excision during a period of 4.3 years following local excision of the primary tumor in the pectoral muscle. The twelfth recurrence was treated by a forequarter amputation. Subsequently, three local recurrences developed in the amputation site during the next 11 years and were treated by wide local exci-

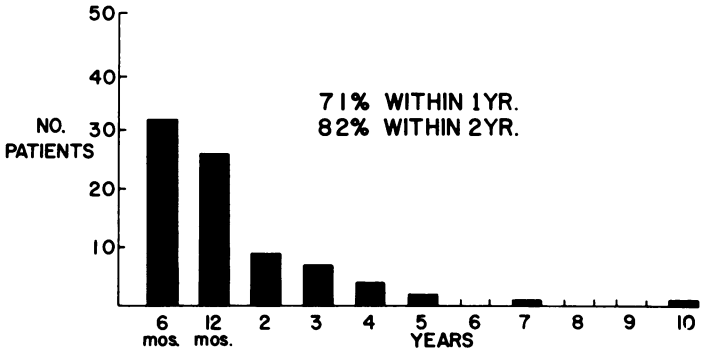

FIG. 2. This diagram illustrates the time interval until local recurrences were detected following the initial surgical treatment of the primary lesion. Seventy-one per cent occurred within one year.

TABLE 3. *Variant Biological Interaction of Rhabdomyosarcoma and the Patient*

Case Hx J.R. 56 W.M. Site-Pectoral Muscle	Case Hx M.M. 66 W.M. Site-Anterior thigh
Local Excision (1/25/53)	Biopsy (5/17/54)
4 Yrs. 3 Mo. — 11 Separate local recurrences and local excisions	Hip disarticulation 5/18/54
12th Local recurrence 4/2/57	1st Recurrence Distant-pulmonary 5-Mo.
Forequarter amputation 5/14/57	
10 Yrs. 11 Mo. — 3 Local recurrences and wide local excisions	Died disease 1/1/55 Since Dx 7 Mo.
Pulmonary Metastasis 4/15/68	
7 Mo.	
Died disease 8/5/68 Since Dx 15 Yrs. 8 Mo.	

sions. In 1968, pulmonary metastases were detected followed by progression and death 15.8 years after the initial diagnosis.

The second patient, M.D., a 66-year-old Caucasian man, had a hip disarticulation for a large primary rhabdomyosarcoma in the upper anterior thigh. The first evidence of recurrence was pulmonary metastases at 5 months, later followed by rapid progression and death only 7 months from the time of initial diagnosis.

Forty of the 155 patients underwent radical amputations as the treatment for the primary tumor and/or for subsequent local recurrences, and the survival rates for these patients are summarized in Table 4. These procedures were an integral part of the primary treatment in 23 of the 40 patients. The 5 and 10-year survival rates for these 23 patients including all 4 tumor groups was 43 and 19%. These procedures were performed on 17 patients for recurrences and the 5 and 10-year survival rates from the time of initial diagnosis was 67% and 34%, and from the time of the radical surgical procedure, 47% and 34%. The average 5 and 10-year survival rates for all 40 patients from the time of initial diagnosis was 45% and 26%, respectively.

In this study, residual tumor was confirmed in specimens from 17 of 43 patients, or 40%, who had wide re-excision of recent locally excised tumors. Fifty-two patients had surgical procedures which provided tissue of lymph node bearing areas for histological study. Invasion of lymph nodes by tumor appeared to be a late manifestation of the disease and was confirmed in only 6 (12%) of these 52 patients. In this group, 8 patients were diagnosed by physical examination as having clinically positive nodes, but tumor invasion was confirmed by histologic studies in 2 of the 8 patients.

Fourteen of the 155 patients, or 9%, developed a second primary tumor of a different cell type and these second primary tumors are summarized in Table 5. Of these 14 patients, 4 are living free of disease from 6 to 15 years following surgical treatment for both primary tumors.

Survival following dissemination or an unresectable state of these sarcomas was short, as outlined in Fig. 3. Of 82 patients with disseminated disease treated with

TABLE 4. *Survival of Sarcoma Patients Following Radical Amputations*

Surgical Procedure	# Pts.	Treatment for Primary Lesion Survival	# Pts.	Treatment for Subsequent Local Recurrence Survival from Time of Amputation
Hemipelvectomy	13	6 died disease 10 mo to 1.8 yrs 1 died no tumor (coronary) 3 yrs 1 living NED* 4.6 yrs 5 living NED > 5 yrs (2/5 pts. living NED > 10 yrs)	5	3 died disease 1 yr to 3.4 yrs 1 died no tumor 3.6 yrs 1 died disease 8.7 yrs
Forequarter	4	1 died disease 5.5 yrs 1 living NED 9.3 yrs 1 living NED 11 yrs 1 living NED 16.4 yrs	10	3 died disease 4 mo to 3.4 yrs 1 died no tumor (CVA) 10.8 yrs 1 died disease 11.3 yrs 1 died disease 14 yrs 1 living NED 2.2 yrs 3 living NED > 5 yrs (2/3 > 10 yrs)
Disarticulation	6	4 died disease 7 mo to 1.3 yrs 1 died post-op CVA 1 mo 1 living NED 2 yrs	2	1 died disease 7 mo 1 living NED 3.8 yrs
Total	23	5 yr survival rate 43%** 10 yr survival rate 19%**	Total 17	5 yr survival rate 47%** 10 yr survival rate 34%**

*NED = no evidence of disease
**Does not include two patients living NED < 5 years.

TABLE 5. *Second Primaries of Different Cell Type*

# PATIENTS	SITE OF TUMOR
6	G.I./or Biliary Tract
4	Breast
2	Brain
2	Urinary Tract
14/155 Patients (9%)*	

*4/14 Pts. living 6-15 years

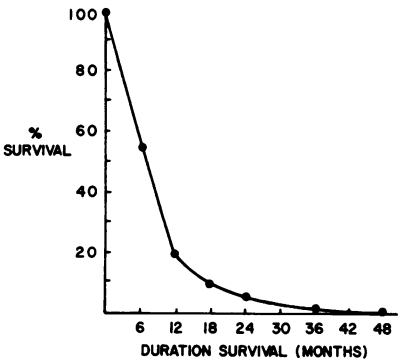

FIG. 3. This figure illustrates the survival of 82 patients with soft tissue sarcomas following an unresectable state treated with chemotherapy and/or radiation therapy.

chemotherapy and/or radiation therapy, 65 or 80% of these patients were dead within one year.

Comment

Soft tissue sarcomas are difficult malignancies to control at the primary site.[2,3,8,9] This series of 155 patients re-emphasizes this problem by a local recurrence rate of: 1) 93% after local excision of the primary lesion; 2) 88% following local excision of the first surgically treatable local recurrence; and 3) an average 53% following all initial surgical therapies for the primary lesion. This Institution provides consultation and therapy for many patients and this high incidence of local recurrence is a reflection of the referral pattern of the Institute. Even so, figures of 93% and 88% illustrate the futility of repeated local excisions as adequate operations when there is still a chance of cure.

Failure of "conservative" local excisions would be anticipated by the histologic confirmation of residual tumor in specimens from 17 of 43 patients (40%) who had wide re-excisions of recently locally excised lesions. The incidence of local recurrence in patients with wide re-excisions was 73%. This figure of 73% and a local recurrence rate following initial wide excision of the primary lesion of 60% indicates the need for more radical procedures, since these malignancies characteristically have direct extension of neoplastic cells for long distances along muscle and nerve bundles and fasial sheaths.

In this series, amputation was the most efficient procedure for controlling the primary site. The initial definitive surgical treatment of the primary tumor was a major and/or a radical amputation in 38 patients. Of these 38 patients, only 3 patients (8%) developed a local recurrence. Of the 83 patients with a first local recurrence, 11 patients were treated by amputations (major and radical) and 2 (18%) of this group developed local recurrence. Although this group is small, the 18% incidence of local recurrence following major amputations for subsequent recurrences indicates the increasing difficulty of controlling the primary lesion.

In addition, failure to control the tumor at the primary site by the first operation affects the overall prognosis, since in this series there was an approximate 30% incidence of distant metastasis occurring following all subsequent treatable local recurrences.

This series of patients with soft tissue sarcomas illustrates, as others have reported[4,9,11,16] several specific surgical principles and techniques which must be followed to achieve maximal long-term survival and cure, namely: 1) an adequate biopsy of every persistent soft tissue mass for histologic evaluation. The biopsy may be by excision if the tumor mass is small, or by core needle, or incision. The biopsy site should be placed within an area which will be included in a definitive cancer operation and the specimen should be given immediately to the pathologist for (a) confirmation that adequate tissue was removed for study and (b) when feasible, a histologic diagnosis by frozen section. 2) If a definitive diagnosis can be made by frozen section, proceed with the previously planned radical surgical excision of the lesion. However, if *any* uncertainty exists as to the diagnosis of an initial lesion by frozen section, the biopsy wound should be closed and the definitive surgical procedure delayed until after study of paraffin sections. 3) The operative procedure must be based on several factors such as anatomic location, size of lesion, depth of invasion, and fixation or nonfixation to vital structures. When an adequate 5-6 cm three dimensional margin of normal tissue cannot be removed, then, in general, amputation proximal to the effected limb segment is best. A forequarter or hemipelvectomy would appear to offer the best hope for cure in those patients with deep lesions, without evidence of distant metastasis, in the upper thigh, groin, buttock, and shoulder areas. 4) Local recurrence without distant spread should be considered potentially curable and proximal amputation is indicated whenever feasible. Lesser procedures performed following local recurrences must be considered more radical and entail more risk to the patient. 5) Growth of tumor tissue in lymph nodes appears to be a late phenomenon and, therefore, prophylactic excision of the regional nodes is unnecessary unless the primary lesion is in juxtaposition (10-15 cm) to them. 6) Patients with soft part sarcomas should have an examination and chest x-ray at 3 month intervals for the first 2 years, then every 6 months through the first 10 years, and yearly thereafter for detection, of local or distant recurrent disease and/or second primaries. 7) Local recur-

rences may occur after disease-free intervals or more than 10 years. These and single distant recurrences, or second primaries, should be considered potentially curable and appropriate therapy carried out.

Radiation Therapy

Our experience with postoperative adjuvant radiation therapy is limited and cannot be evaluated. Various degrees of tumor regression and pain relief were observed in several of our patients with non-resectable liposarcoma and embryonal rhabdomyosarcoma.

Several retrospective studies provide evidence that soft tissue sarcomas in many patients are responsive to radiation therapy.[6,10,12,13,15,17] The cure rate following combined treatment with radiation and surgery was significantly higher than that observed with only surgery.[10,17] Amputation of extremities was avoided in several of these patients.[17] These data support the need for prospective clinical studies of combination therapy.

Chemotherapy and Immunotherapy

Thirty-six of the 155 adult patients received chemotherapy for disseminated disease. These agents included dactinomycin, cyclophosphamide, vincristine, nitrogen mustard, thio-tepa, and cytosine arabinoside administered singly or in combination without a clinically significant antitumor effect. Several recent reports[1,5,18] indicate antitumor effect of adriamycin used alone or in combination with dimethyl triazeno imidazole carboxamide. Prognosis of children with solid tumors has been significantly improved with a combination of surgery, radiation, and maintenance multiple chemotherapy.[7,14] These reports are encouraging and further studies of multimodality therapy may improve the overall survival rates of adult patients with soft tissue sarcomas.

The risk of dangerous immunosuppression with chemotherapy must be balanced against the theoretical destruction of residual tumor cells. Immunotherapy rarely provides spectacular tumor regressions but it can be used as an adjuvant to local therapy with undue risk.

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